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(54) Title: TOPICAL AGENT FOR DERMATOLOGICAL USE

(57) Abstract: The objective of the present invention was to enhance the skin whitening effects and blackening prevention effects and supply safe and stable topical agents for dermatological use. For that purpose 4-Hydroxyphenyl- α -D-glucopyranoside was combined with auxiliary agents such as ascorbic acid and its derivatives, crude drugs and its extracts, hydroxycarboxylic acid and its salts, oil soluble glycyrrhiza extract, gentian extract, phenol derivatives and their salts, placenta extract, kojic acid and its derivatives, glucosamine and its derivatives, azelaic acid and its derivatives, retinol and its derivatives, pyridoxin and its derivatives, tocopherol and its derivatives, chitosan and its decomposition products, caffeic acid derivatives, hydroxycinnamate and its derivatives, Umbelliferae plant extracts, mycelial cultures and their extracts, plant leaves and their extracts.

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Topical agent for dermatological use

5 0001

Art to which the invention pertains

The present invention is related to topical agents for dermatological use which whiten the skin color or prevent its blackening and prevent or relieve liver spots, freckles, etc. and which show generally desirable formulation properties in terms of the safety and stability.

15 0002

Conventional technology

Various melanin formation preventing agents have been used to whiten the skin color or prevent its blackening and prevent or relieve skin troubles such as liver spots and freckles caused due to excessive exposure to UV rays. These agents include 1,4-dihydroxybenzene, β -arbutin, vitamin C and its derivatives, and kojic acid.

25 0003

However, vitamin C, 1,4-dihydroxybenzene and kojic acid are extremely unstable with respect to heat and oxidation in water. When added to topical agents for dermatological use, therefore, these compounds decompose over time and cause coloration. Their derivatives, such as phosphate-ascorbyl magnesium and β -arbutin, which is

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obtained as a result of the β -binding of glucose to one of the hydroxy groups of 1,4-dihydroxybenzene, are not necessarily satisfactory in terms of efficacy although they are more stable than their parent compounds with
5 respect to heat and oxidation.

0004

To overcome this problem, various inventions have been
10 made and applications for patents have been submitted, such as cosmetics which contain, in addition to β -arbutin, ingredients with skin whitening effects, such as UV absorbents, anti-inflammatory agents, and placenta extracts, so that synergistic effects can be obtained
15 (e.g., Toku-kai-hei 5-186324 Patent Gazette) and topical agents for dermatological use which contain pantethine-S-sulfonic acid or its salt and which prevent decomposition and coloration over time (Toku-kai-hei 5-58926 Patent Gazette). However, these substances cannot be added to
20 cosmetic products in a quantity large enough to obtain clinically significant synergistic effects due to problems related to safety and bad feeling experienced upon contact with the skin.

25 0005

The authors of the present invention looked for substances which are stable when used in topical agents for dermatological use and which are safer and more effective
30 than conventional compounds. In this effort, they discovered 4-hydroxyphenyl- α -D-glucopyranoside as a substance which satisfies these requirements and have

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applied for a patent (Tokugan 2000-43366). However, its efficacy had to be further improved in order to expect clinically significant whitening effects.

A patent has been disclosed for amylase X-23 as an
5 enzyme which transfers sugars to the phenol group of 1,4-dihydroxy-benzene through α -binding (Patent No. 2662667).

0006

10 Problems which the present invention is designed to solve

As mentioned above, various attempts have been made to enhance skin whitening effects, but none has been found satisfactory. The present invention uses 4-hydroxyphenyl- α -D-gluco-pyranoside, which shows marked skin whitening
15 effects even when used alone, and add other substances which enhance or supplement its effects to produce topical agents with dermatological use which are more effective than conventional products.

20 0007

Methods used to solve the problems

The authors of the present invention conducted studies to solve the above-mentioned problems, found that the
25 combination of 4-hydroxyphenyl- α -D-glucopyranoside and specific ingredients (hereafter sometimes referred to as "auxiliary ingredients") results in a marked enhancement of the effects of 4-hydroxyphe-nyl- α -D-glucopyranoside, which shows far greater skin whitening effects than conventional
30 products even when used alone, and completed the present invention.

0008

The present invention pertains to topical agents for derma-tological use which are characterized by the fact
5 that they contain 4-hydroxyphenyl- α -D-glucopyranoside and at least one auxiliary ingredient like e.g. one of the following: ascorbic acid and its derivatives, crude drugs and their extracts, hydroxycarboxylic acid and its salts, oil-soluble glycyrrhiza extract, gentian extract, phenol
10 derivatives and its salts, placenta extract, kojic acid and its derivatives, glucos-amine and its derivatives, azelaic acid and its derivatives, re-tinol and its derivatives, pyridoxin and its derivatives, toco-pherol and its derivatives, vitamin E-nicotinate, diisopropyl-amine-
15 dichloroacetate, chitosan and its decomposition products, caffeic acid derivatives, hydroxycinnamate and its derivatives, Umbelliferae plant extracts, mycelial cultures and their extracts, plants leaves and their extracts, plant bark and its extracts, hinokitiol, ginseng extract, sulfur,
20 crude sugar extracts, molasses extracts, mucopolysaccharide, teprenone, nordihydroguaiaretic acid, UV absorbents, γ -pyrone glycoside, hydroxysalicylic acid glycoside, hydroxysalicylic acid fatty ester glycoside, biphenyl compounds, ceramides, substances with ceramide-like structures, ether compounds which can be shown by the
25 general formula R31-O-(X-O)n-R32 (in which R31 and R32 are the same or different normal-chain, branched or cyclic alkyl groups with 1 to 12 carbon atoms, X is alkylene groups with 1 to 12 carbon atoms, n is 0 or 1, and the number of synthetic carbon atoms in R31, R32 and X is 10 to
30 32), pantothenic acid and its derivatives, sodium hydrogen sulfite, antiinflammatory agents, allantoin and its

- 5 -

derivatives, amino acid and its derivatives, amino ethyl compounds, alkylene diamine carboxylic acid derivatives, betaine derivatives, acyl methyl taurine, fibronectin, tyrosinase inhibitors, hederacoside and its salts, gymnema saponin, beat saponin and its salts, ellagic acid-related compounds and their alkaline metallic salts, and resorcinol derivatives. It also pertains to topical agents for dermatological use described above which are characterized by the fact that 4-hydroxyphenyl- α -D-glucopyranoside is obtained using α -amylase, as well as those in which α -amylase is amylase X-23.

0009

15 Working of the invention

The auxiliary agents under the present invention, when at least one of them is added to topical agents for dermatological use in combination 4-hydroxyphenyl- α -D-glucopyranoside, increase whitening effects or stability of 4-hydroxyphenyl- α -D-glucopyranoside. Explanations of these auxiliary agents are provided below.

0010

25 Among various types of ascorbic acid, L-ascorbic acid, generally called vitamin C, promotes cell respiration, enzymatic activation, and collagen formation due to its strong reducing effects and also reduces melanin. Derivatives of ascorbic acid include ascorbate 30 monoalkylesters (such as ascorbate monostearate, ascorbate monopalmitate and ascorbate monooleate), ascorbate monoester derivatives (such as ascorbate monophosphate

- 6 -

ester and ascorbate-2-sulfate), ascorbate diester derivatives (such as ascorbate distearate, ascorbate dipalmitate, ascorbate dioleate and ascorbate diphosphate esters), ascorbate trialkyl esters (such as ascorbate 5 tristearate, ascorbate tripalmitate and ascorbate trioleate), and ascorbate triester derivatives (such as ascorbate triphosphate ester).

Efficacy is seen when these ingredients are added at 0.01 w/w% or more in topical agents for dermatological use.
10 The upper limit of content is about 10%.

0011

Usable crude drugs include the following and their
15 extracts can also be used: mulberry bark, peony root, scutellaria root, chamomile, Japanese angelica root, rosemary, geranium herb, lithospermum root, tea leaf, pueraria root, clove, glycyrrhiza, biwa, bitter orange peel, ginseng, sanzasi, ophiopogon tuber, ginger, pine
20 cone, magnolia bark, gambir, aloe, marshmallow, meadow sweet, water cress, cinchona, comfrey, scopolia rhizome, swertia herb and yarrow (*Achillea millefolium Linn'e*) (Composi-tae). Under the present invention, crude drugs and their ex-tracts include fine power obtained by
25 pulverizing (and drying, if necessary) the whole plants, roots, leaves, flowers, seeds, etc. of the above mentioned crude drugs, extracts obtained by soaking these materials in water and/or organic solvents and filtering the residue, fluid obtained by removing the solvent from these extracts,
30 and these power products or extracts with or without the solvents dissolved, dispersed, or diluted with appropriate solvents or dissolving agents.

The content of these materials in topical agents for

- 7 -

dermatological use should be 0.001-20 w/w%, preferably 0.01-10 w/w%.

0012

5

Hydroxycarboxylic acids include glycollic acid, lactic acid, malic acid, tartaric acid, citric acid, salicylic acid, mevalonic acid, and lactone mevalonate. Their salts include metallic salts such as Na, K and Mg, as well as 10 organic salts such as triethanolamine and 2-amino-2-methyl-1,3-propandiol.

The content of these ingredients in topical agents for dermatological use should be 0.0001-5 w/w%, preferably 0.001-3 w/w%.

15

0013

Oil-soluble glycyrrhiza extracts are obtained by extracting glycyrrhiza (*Glycyrrhizaglabra* linne), a 20 perennial legume, with lower monohydric alcohol such as methyl alcohol and ethyl alcohol and fluid polyhydric alcohol such as glycerin, propylene glycol, and 1,3-butylene glycol. Any preparation method may be used, e.g., extraction using various appropriate solvents at low temperature or room temperature or with heating. Preferably, extraction should be conducted as follows: extract with ethyl alcohol for 2-10 hours while heating; filter; allow the obtained filtrate to stand for 2 to 3 days and allow it 25 to mature; and filter again. The extract obtained may be condensed and dried, if necessary, after extraction with heating. Oil-soluble glycyrrhiza extracts thus obtained are a brown substance with a peculiar odor. They can be 30 used as is in many cases but may be deodorized or

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decolorized to purify them, if necessary, as long as their efficacy is not compromised. Purification may be conducted using, for example, an active carbon column. Any method commonly applied to extracts may be used for purification.

5 The content may vary between 0.0001 and 5% w/w%, preferably between 0.001 and 3% w/w%, depending on the quality of the extract used and other factors.

0014

10

Gentian extracts can be obtained by extracting the root and rhizome of gentian (*Gentiana lutea* linne (Gentianaceae)), a plant which belongs to the Gentianaceae family, with lower monohydric alcohol such as methyl 15 alcohol and ethyl alcohol and fluid poly-hydric alcohol such as glycerin, propylene glycol, and 1,3-butylene glycol. Any preparation method may be used, e.g., extraction using various appropriate solvents at low temperature or room temperature or with heating. 20 Preferably, extraction should be conducted as follows: extract with 50% 1,3-butylene glycol in water for 2-10 hours while heating; filter; allow the obtained filtrate to stand for 2 to 3 days and allow it to mature; and filter again. The extract obtained may be condensed and dried, if 25 necessary, after extraction with heating.

The content may vary between 0.0001 and 5% w/w%, preferably between 0.001 and 3% w/w%, depending on the quality of the extract used and other factors.

30 0015

Phenol derivatives and its salts include 4-ethoxyphenol, 4-n-propoxyphenol, 4-n-butoxyphenol, 4-n-

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hexadecyloxyphenol, 4-n-octadecyloxyphenol, 4-ethylphenol,
4-n-propylphenol, 4-n-butyl-phenol, 4-t-butylphenol, 4-
isopropylphenol, 4-hexadecylphenol, 4-octadecylphenol, 4-
isopropylcatecholmonocutylester, and 4-isopro-
5 pylcatecholmonoheptadecaester.

The content may vary between 0.01 and 20% w/w%, preferably between 0.1 and 10% w/w%, in topical agents for dermatological use.

10 0016

Placenta extracts include extracts obtained by soaking the placenta from humans, monkeys, cows, pigs, sheep, mice and other animals in water and/or organic solvents and
15 filtering the residue, fluid obtained by removing the solvent from these extracts, and power of these placenta or the above-mentioned extracts with or without the solvents dissolved, dispersed, or diluted. Specifically, these placenta extracts are commercially available as water or
20 oil-soluble placenta extracts.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0017

25

Kojic acid and its derivatives include monoesters such as kojic acid, kojic acid glycoside, kojic acid monobutyrate, kojic acid monocaprate, kojic acid monopalmitate, kojic acid monostearate, kojic acid
30 monocinnamate, and kojic acid monobenzoate, as well as diesters such as kojic acid dibutyrate, kojic acid dipalmitate, kojic acid distearate, and kojic acid dioleate.

The content in topical agents for dermatological use

- 10 -

should be 0.001-30 w/w%, preferably 0.01-10 w/w%, and more preferably 0.01-5 w/w%.

0018

5

Glucosamine and its derivatives include glucosamine, glucosamine-6-phosphate, and glucosamine-6-sulfate.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

10

0019

Azelaic acid and its derivatives include azelain and azelaic acid.

15

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0020

20

Retinol is generally called vitamin A1 and is effective in maintaining normal function of the skin and mucosa. Its derivatives include retinal and retinoic acid.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

25

0021

Pyridoxin is a substance with vitamin B6 effects, and its derivatives include pyridoxal, pyridoxamine, pyridoxin-30 5'-phosphate, pyridoxal-5'-phosphate, pyridoxamine-5'-phosphate, pyridoxal phosphate, and pyridoxic acid.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

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0022

5 Tocopherol, a group of vitamin E derivative, is effective in preventing and treating hyperkeratosis and other diseases and preventing and reversing aging of the skin. This group includes α -tocopherol, β -tocopherol, γ -tocopherol and δ -tocopherol. Their derivatives may also be
10 used in the present invention

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0023

15

Alpha-tocopherol derivatives include α -tocopheryl retinoate, which is vitamin A acid ester. Here, α -tocopherol refers to DL- α -tocopherol, D- α -tocopherol or mixed natural tocopherol containing D- α -tocopherol.
20 Vitamin A acid refers to retinoic acid (all-trans-retinoic acid), 13-cis-retinoic acid, 11-cis-retinoic acid, 9-cis-retinoic acid or their mixed isomers. Ester of DL- α -tocopherol and all-trans-retinoic acid is particularly preferable.

25

0024

Vitamin E-nicotinate and diisopropylamine dichloroacetate improve blood flow, activate cells, inhibit the formation of melanin due to UV rays, promote the elimination of melanin, prevent epidermal drying, accelerate skin metabolism, and prevent aging of the skin

- 12 -

due to UV rays.

The content of vitamin E-nicotinate or diisopropylamine dichloroacetate in topical agents for dermatological use should be 0.01-5 w/w%.

5

0025

Chitosan is produced as a result of deacetylation of chitin and has a β -1,4-polyglucosamine structure.

10 Decomposition products of chitosan are obtained as a result of treatment of chitosan with enzymes such as chitinase and contain glucosamine and its oligomers.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

15

0026

The content of caffeic acid derivatives in topical agents for dermatological use should be 0.001-5 w/w%,

20 preferably 0.1-3 w/w%.

0027

Hydroxycinnamate and its derivatives include hydroxycinnamic acid (including p-coumarinic acid and p-coumaric acid) and caffeic acid.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

30 0028

Umbelliferae plant extracts include extracts obtained

- 13 -

by soaking the whole plants, roots, leaves, flowers, seeds, etc. of umbelliferae plants (such as ledebouriella, glehnia root, Noto-pterygium incisum Ting, cnidium rhizome, angelica dahurica root, Ligusticum sinense Oliv., dokkatu, 5 zenko and bupleurum) in water and/or organic solvents and filtering the residue, fluid obtained by removing the solvent from these extracts, and these power products or extracts with or without the solvents dissolved, dispersed, or diluted with appropriate solvents or dissolving 10 agents.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0029

15

Mycelial cultures refer to mycelia of mushroom and reisi cultured on appropriate media and include culture fluid itself in the case of liquid culture and mycelia pulverized after drying, etc., if necessary, in the case of 20 solid culture. Extracts of mycelial cultures include extracts obtained by soaking the above-mentioned mycelial cultures, mycelia or their powder in water and/or organic solvents and filtering the residue, fluid obtained by removing the solvent from these extracts, and these power 25 products or extracts with or without the solvents dissolved, dispersed, or diluted with appropriate solvents or dissolving agents.

The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

30

0030

Plant leaves include leaves from plants such as apple,

- 14 -

Japanese pieris, amasiba (Japanese name), and gymnema. Leaves are pulverized after drying, if necessary. Extracts of plant leaves include extracts obtained by soaking these leaves or their powder in water and/or organic solvents and 5 filtering the resi-due, fluid obtained by removing the solvent from these extracts, and these power products or extracts with or without the solvents dissolved, dispersed, or diluted with appropriate solvents or dissolving agents.

The content in topical agents for dermatological use 10 should be 0.001-20 w/w%, preferably 0.1-3 w/w%.

0031

15

Plant bark includes the bark from trees of fruits such as apple, cherry, peach, and pear. The bark is pulverized after drying, if necessary. Extracts of the bark include extracts obtained by soaking the bark or its powder in 20 water and/or organic solvents and filtering the residue, fluid obtained by removing the solvent from these extracts, and these power products or extracts with or without the solvents dissolved, dispersed, or diluted with appropriate solvents or dissolving agents.

25 The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0032

30 The content of hinokitiol in topical agents for dermatologi-cal use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0033

Ginseng extracts include extracts obtained by soaking gin-seng or its powder in water and/or organic solvents and 5 filtering the residue, fluid obtained by removing the solvent from these extracts, and these power products or extracts with or without the solvents dissolved, dispersed, or diluted with appropriate solvents or dissolving agents. These extracts are commercially available.

10 The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0034

15 The content of sulfur in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%.

0035

20 Crude sugar extracts are brown pigment ingredients. Dried power is hygroscopic and has a slight burning odor and a slight bitter taste. Their production methods are described in Toku-Kai-Sho No. 60-78912 Patent Gazette. 25 Specifically, crude sugar (black sugar) or molasses (by-product obtained in the production of white sugar from black sugar) is dissolved in an appropriate amount of water, and pigment ingredients are adsorbed by bringing them into contact with adsorbents such as non-polar 30 polystyrene resin adsorbents. Adsorbents are washed with water to thoroughly eliminate sugar. The pigment ingredients adsorbed to the adsorbents are eluted with hydrous alcohol of 20% or higher concentrations. After

- 16 -

condensation or freeze drying, the pigment ingredients are refined by recrystallization, if necessary, by evapo-rating the ingredients to dryness.

The content in topical agents for dermatological use
5 should be 0.01-10 w/w%, preferably 0.1-5 w/w%.

0036

Molasse extract's main ingredient is oligosaccharide
10 and can be obtained by soaking molasses in cold or warm lower alcohol such as methanol and ethanol and filtering, condensing and discoloring the fluid obtained.

The content in topical agents for dermatological use
should be 0.01-10 w/w%, preferably 0.1-5 w/w%.

15

0037

Mucopolysaccharide shows skin moisturizing effects and includes hyaluronic acid, chondroitin-4-sulfate, chondroitin-6-sulfate, dermatan sulfate, heparin and their salts.

The content in topical agents for dermatological use
should be 0.001-10 w/w%, preferably 0.01-5 w/w%.

0038

25

Teprenone, chemically named geranyl geranyl acetone, protects the mucosa and promotes its repair, activates cell growth, and accelerates the synthesis of phospholipid. Teprenone was also found to inhibit tyrosinase, an enzyme 30 involved in the biosynthesis of melanin which causes liver spots, freckles, and black skin (Toku-Kai-Hei No. 6-16532 Patent Gazette).

The content in topical agents for dermatological use

- 17 -

should be 0.01-20 w/w%, preferably 0.5-10 w/w% and more preferably 1.0-10 w/w%.

0039

5

Nordihydroguaiaretic acid, generally known as an antioxidant and a lipoxygenase inhibitor, is added to cosmetic and pharmaceutical products to prevent oxidation and stabilize formulations.

10 The content in topical agents for dermatological use should be 0.001-10 w/w%, preferably 0.1-5 w/w%.

0040

15 Any UV absorbents commonly used in topical agents for dermatological use can be used as UV adsorbents in the present invention. Typical UV adsorbents are listed below.

0041

20

1) Benzoate UV absorbents

Paraaminobenzoic acid (PABA), PABA monoglycerin ester, N,N-bis-(3-hydroxypropyl) PABA ethyl ester, N,N-bis-(2-hydroxyethyl) PABA ethyl ester, N,N-dimethyl PABA ethyl ester, N,N-dimethyl PABA butylester, N,N-dimethyl PABA amylester, and N,N-dimethyl PABA octyl ester.

0042

30 2) Anthranilate UV absorbents

Homomenthyl-N-acetylanthranilate

0043

3) Salicylate UV absorbents

Amylsalicylate, methylsalicylate,
homomenthylsalicylate, octylsalicylate, phenylsalicylate,
benzylsalicylate, and 4-
isopropylphenylsalicylate

0044

10 4) Cinnamate UV absorbents

Octylcinnamate, ethyl-4-isopropylcinnamate, methyl-
2,5-diisopropylcinnamate, ethyl-2,4-diisopropylcinnamate,
methyl-2,4-diisopropylcinnamate, propyl-4-methoxycinnamate,
isopropyl-4-methoxycinnamate, isoamyl-4-methoxycinnamate,
15 isopropyl-4-methoxycinnamate, isoamyl-4-methoxycinnamate,
octyl-4-methoxy-cinnamate (2-ethylhexyl-4-
methoxycinnamate), 2-ethoxyethyl-4-methoxycinnamate,
cyclohexyl-4-methoxycinnamate, ethyl- α -cyano- β -
phenylcinnamate, 2-ethylhexyl- α -cyano- β -phenylcinnamate,
20 and glyceryl mono-2-ethylhexanoyl-bis-
(paramethoxycinnamate)

0045

25 5) Benzophenone UV absorbents

2,4-dihydroxybenzophenone, 2,2'-dihydroxy-4-
methoxybenzo-phenone, 2,2'-dihydroxy-4,4'-
dimethoxybenzophenone, 2,2'-4,4'-tetrahydroxybenzophenone,
2-hydroxy-4-methoxy-benzophenone, 2-hydroxy-4-methoxy-4'-
30 methylbenzophenone, 2-hydroxy-4-methoxy-benzophenone-5-
sulfonate, 4-phenylbenzophenone, 2-ethylhexyl-4'-
phenylbenzophenone-2-carboxylate, 2-hydroxy-4-n-

- 19 -

octoxybenzo-phenone, and 4-hydroxy-3-carboxybenzophenone.

0046

5 6) Other UV absorbents

3-(4'-methylbenzylidene)-d,l-camphor, 3-benzylidene-d,l-camphor, urocanic acid, ethyl urocanate, 2-phenyl-5-methylbenz-oxazol, 2-(2'-hydroxy-5'-ethylphenyl)-benzotriazol, 2-(2'-hydroxy-5'-t-butylphenyl)-benzotriazole, 2-(2'-hydroxy-5'-methylphenyl)-benzotriazole, dibenzalazine, dianisoylmethane, 4-methoxy-4'-t-butyldibenzoylmethane, 5-(3,3-dimethyl-2-norbornylidene)-3-pentane-2-one.

15 0047

The content in topical agents for dermatological use should be 0.01-10 w/w%, preferably 0.5-8 w/w%. If the content is too small, sunburn can not be prevented and the 20 whitening effects of 4-hydroxyphenyl- α -D-glucopyranoside are reduced. If the content is too large, stability of topical agents for dermatological use is affected.

0048

25

γ -Pyrone glycoside prevents liver spots and freckles due to sunburn. It is maltol-3-O-(6'-O-apiocil)-glucoside or maltol-3-O-glucoside which can be shown by general formula 1 shown below. For example, it can be collected by 30 column chromatography, HPLC, TLC, etc. from pueraria root extracts.

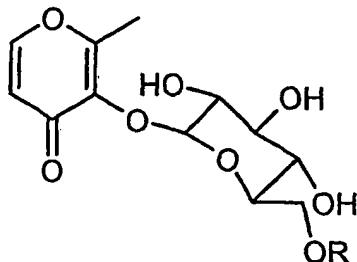
The content in topical agents for dermatological use

- 20 -

should be 0.00001-2.5 w/w%, preferably 0.0001-1 w/w%.

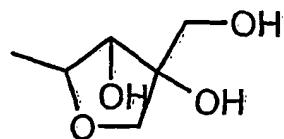
0049

5 Chemistry 1



General formula 1

10 In the above formula, R is a hydrogen atom or the group shown below.



15 0050

Hydroxysalicylic acid glycoside and hydroxysalicylic acid fatty ester glycoside show excellent whitening effects as a result of synergism with 4-hydroxyphenyl- α -D-glucopyranoside and can be shown by general formulas 2, 3 and 4.

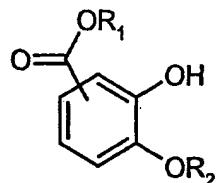
These glycosides can be obtained by allowing hydroxysalicylic acid or hydroxysalicylic acid fatty ester to react with acetylated sugar such as pentaacetylglucose (or aceto-bromated sugar such as acetobromoglucose) in the presence of acidic catalysts.

The content in topical agents for dermatological use

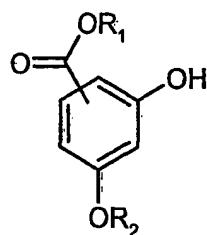
- 21 -

should be 0.001-20 w/w%, preferably 0.1-7 w/w%.

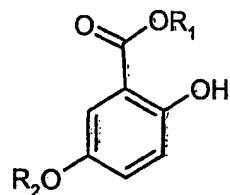
0051
5 Chemistry 2



10 General formula 2



General formula 3



General formula 4

15
0052

In general formulas 2 through 4, R1 is a hydrogen atom or saturated or unsaturated normal-chain or branched 20 hydrocarbon group with 1 to 20 carbon atoms, while R2 is a sugar residue.

0053

Examples of the above-mentioned glycosides are listed below.

- 5 3- β -D-glucopyranosyloxy salicylic acid, 3- β -D-glucopyranosyloxy methyl salicylate, 3- β -D-glucopyranosyloxy ethyl salicylate, 3- β -D-glucopyranosyloxy propyl salicylate, 3- β -D-glucopyranosyloxy isopropyl salicylate, 4- β -D-glucopyra-nosyloxy salicylic acid, 4- β -D-
- 10 10 glucopyranosyloxy methyl salicylate, 4- β -D-gluco-pyranosyloxy ethyl salicylate, 4- β -D-glucopyranosyloxy propyl salicylate, 4- β -D-glucopyrano-syloxy isopropyl salicylate, 5- β -D-glucopyranosyloxy salicylic acid, 5- β -D-glucopyranosyloxy methyl salicylate, 5- β -D-
- 15 15 glucopyranosyloxy ethyl salicylate, 5- β -D-glucopyranosyloxy propyl salicylate, 5- β -D-glucopyranosyloxy isopropyl salicylate, 6- β -D-glucopyranosyloxy salicylic acid, 6- β -D-glucopyranosyloxy methyl salicylate, 6- β -D-glucopyranosyloxy ethyl salicylate, 6- β -D-glucopyranosyloxy
- 20 20 propyl salicylate, 6- β -D-glucopyranosyloxy isopropyl salicylate, 2- β -D-glucopyrano-syloxy-3-hydroxybenzoic acid, 2- β -D-glucopyranosyloxy-3-methyl hydroxybenzoate, 2- β -D-glucopyranosyloxy-3-ethyl hydroxybenzo-ate, 2- β -D-glucopyranosyloxy-3-propyl hydroxybenzoate, 2- β -D-
- 25 25 glucopyranosyloxy-3-isopropyl hydroxybenzoate, 2- β -D-glucopyra-nosyloxy-4-hydroxybenzoic acid, 2- β -D-glucopyranosyloxy-4-methyl hydroxybenzoate, 2- β -D-glucopyranosyloxy-4-ethyl hydroxybenzo-ate, 2- β -D-glucopyranosyloxy-4-propyl hydroxybenzoate, 2- β -D-
- 30 30 glucopyranosyloxy-4-isopropyl hydroxybenzoate, 2- β -D-glucopyra-nosyloxy-5-hydroxybenzoic acid, 2- β -D-

- 23 -

glucopyranosyloxy-5-methyl hydroxybenzoate, 2- β -D-glucopyranosyloxy-5-ethyl hydroxybenzo-ate, 2- β -D-glucopyranosyloxy-5-propyl hydroxybenzoate, and 2- β -D-glucopyranosyloxy-5-isopropyl hydroxybenzoate

5

0054

Biphenyl compounds inhibit tyrosinase activity and melanin formation and can be shown by general formulas 5
10 and 6.

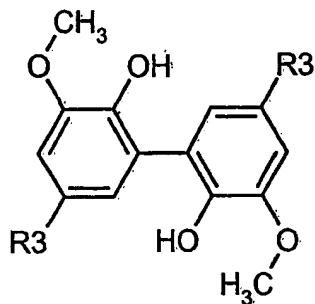
Specifically, biphenyl compounds include dehydrocreosol, dehydronieugenol, and tetrahydromagnolol.

The content in topical agents for dermatological use should be 0.0001-20 w/w%, preferably 0.001-5 w/w%.

15

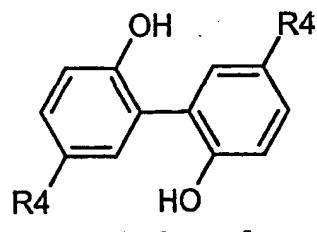
0055

Chemistry 3



20

General formula 5



- 24 -

0056

In general formulas 5 and 6, R3 is CH₃, C₂H₅, C₃H₇, CH₂OH, C₃H₆OH, CH₂CH=CH₂, while R4 is a hydrogen atom or
5 saturated normal-chain or branched hydrocarbon group with 1 to 8 carbon atoms.

0057

10

Ceramides and substances with ceramide-like structures moisten, soften and whiten the skin, alleviate inflammation, antagonize oxidation, and promote blood flow. Ceramides are shown by general formula 7, while substances
15 with ceramide-like structures are shown by general formulas 8, 9, 10, 11, and 12.

Ceramides and substances with ceramide-like structures can be used in combination (combination of 1 or more of the ceramides and/or substances with ceramide-like structures).
20 The content in topical agents for dermatological use should be 0.01-50 w/w%, preferably 0.01-20 w/w% and more preferably 0.1-10 w/w%. These substances show moisturizing effects and prevent and relieve rough skin with good stability and feeling upon contact with the skin.

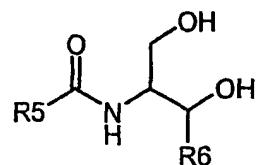
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0058

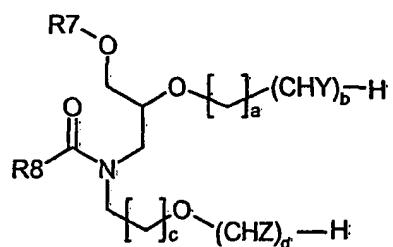
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- 25 -

Chemistry 4

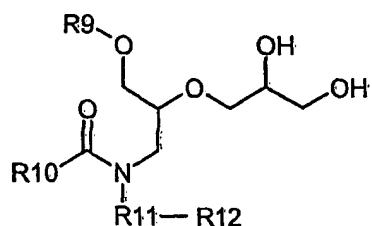


General formula 7



5

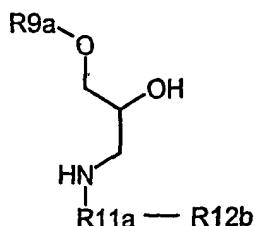
General formula 8



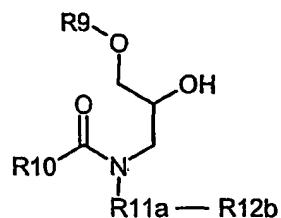
General formula 9

10

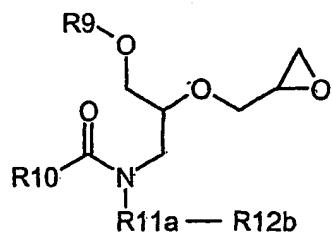
0059



General formula 10



General formula 11



5

General formula 12

10 0060

In general formula 7, R5 and R6 are the same or different hydroxyl group-substituted normal-chain or branched, saturated or unsaturated hydrocarbon groups with 15 8 to 26 carbon atoms.

In general formula 8, R7 is a normal-chain or branched, saturated or unsaturated hydrocarbon group with 10 to 26 carbon atoms; R8 is a normal-chain or branched, saturated or unsaturated hydrocarbon group with 9 to 25 20 carbon atoms; Y and Z are a hydrogen atom or a hydroxyl group; a is 0 or 1; c is an integral number of 0 to 4; and b and d are integral numbers of 0 to 3.

In general formula 9, R9 and R10 are the same or different normal-chain or branched, saturated or 25 unsaturated, hydroxylated or non-hydroxylated hydrocarbon

- 27 -

groups with 1 to 40 carbon atoms; R11 is a normal-chain or branched alkylene group with 1 to 6 carbon atoms or a single bond; and R12 is a hydrogen atom, normal-chain or branched alkoxy group with 1 to 12 carbon atoms or 2,3-dihydroxypropyloxy group. When R11 is a single bond, R12 is a hydrogen atom.

In general formula 10, R9a is a hydroxylated or nonhydroxy-lated hydrocarbon radical with 4 to 40 carbon atoms; R11a is a normal-chain or branched alkylene group with 3 to 6 carbon atoms; and R12a is a normal-chain or branched alkoxy group with 1 to 12 carbon atoms.

In general formula 11, R9, R10, R10a, and R12a are the same as above.

In general formula 12, R9, R10, and R11 are the same as above; and R12b is a hydrogen atom or a normal-chain or branched alkoxy group with 1 to 12 carbon atoms or 2,3-dihydroxypropyloxy group. When R11 is a single bond, R12b is a hydrogen atom.

20

0061

Ether compounds which can be shown by the general formula R21-O-(X-O)_n-R22 increase percutaneous absorption of the topical agents for dermatological use pertaining to the present invention without irritating the skin.

In this general formula, R21 and R22 may be the same or different and are normal-chain, branched or cyclic alkyl groups with 1 to 12, preferably 2 to 22 and more preferably 3 to 20, carbon atoms. It is preferable that R21 and/or R22 are branched at 2 or more sites, preferably at 2 sites. Specifically, these groups include the following:

- 28 -

methyl group, butyl group, n-butyl group, n-decyl group, n-dodecyl group, n-tetradecyl group, n-octadecyl group, n-eicosyl group, n-tetracosyl group, 1-methylpropyl group, 3-methylhexyl group, 2-methylheptadecyl group, 1,3-5 dimethylbutyl group, 1,3-dimethylpentyl group, and cyclopentyl group.

X is an alkylene group with 1 to 12, preferably 1 to 8, carbon atoms, specifically, methylene group, ethylene group, butylene group, etc.

10 The combined number of carbon atoms in R21 and R22 must be 10 to 32, preferably 12 to 28.

n is 0 or 1, preferably 0.

0062

15

These ether compounds can be manufactured by known methods, e.g., direct etherification of corresponding alcohol and alkyl halide, reduction of aryl ether obtained as a result of addition of corresponding alcohol and olefin 20 in the presence of Lewis acid catalyst or as a result of addition of corresponding alcohol and alkyl halide in the presence of alkaline catalyst, and reduction of acetal or ketal produced from corresponding alcohol and aldehyde or ketone.

25 The content in topical agents for dermatological use should be 0.01-50 w/w%, preferably 0.01-20 w/w% and more preferably 0.1-10 w/w%.

0063

30

Pantothenic acid is a vitamin B. It not only shows skin whitening effects but increases stability of 4-

- 29 -

hydroxyphenyl- α -D-glucopyranoside in topical agents for dermatological use. Ist de-rivatives include pantethine-S-sulfonic acid, 4'-phosphopantheti-ne-S-sulfonic acid, pantethine, and glucopyranosyl pantothenate. These 5 compounds can be used in the form of not only free acid but salt as well. Salts include a wide range of organic and inorga-nic acid salts, but alkaline metal salts and alkali earth metal salts, e.g. calcium d-pantetheine-s-sulfonate are preferable.

10 The content in topical agents for dermatological use should be 0.001-5 w/w%, preferably 0.1-3 w/w%. The content should be ad-justed so that the ratio of weight of 4-hydroxyphenyl- α -D-gluco-pyranoside and pantothenic acid and/or its derivatives is not less than 1:0.1, preferably 15 1:0.1 to 10 and more preferably 1:0.5 to 5.

0064

Sodium hydrogen sulfite is known to increase the 20 stability of β -arbutin in topical agents for dermatological use (Patent No. 2107858). Sodium hydrogen sulfite also increase the stability of 4-hydroxyphenyl- α -D-glucopyranoside in topical agents for dermatological use. The content should be adjusted so that 4-hydroxyphenyl- α -D-glucopyranoside:sodium hydrogen sulfite 25 ratio (weight) is 1:0.0001 to 1, preferably 1:0.001 to 0.1.

0065

30 Anti-inflammatory agents are used to prevent inflammation and other adverse reactions that may be caused

- 30 -

by some of the auxiliary agents used in the present invention. Any anti-inflammatory agents applicable to the skin can be used, such as oxyben-zone, tranexamic acid and its derivatives, ϵ -aminocaproic acid, glycyrrhizic acid, 5 azulene, sensitizing agent No. 301, sensitizing agent No. 401, diphenhydramine HCl, adenosine phosphate, calamine, lithospermum root extract, mugwort extract, sargisorba extract, aminocaproic acid and bisabolol.

The content in topical agents for dermatological use 10 should be 0.01-2 w/w%, preferably 0.1-2 w/w%.

0066

Allantoin is used to treat various dermatological 15 diseases and is effective in the treatment of skin wound and prevention of rough skin. Its derivatives include dihydroxy aluminum allantoinate and chlorohydroxy aluminum allantoinate.

The content in topical agents for dermatological use 20 should be 0.01-5 w/w%, preferably 0.1-3 w/w%.

0067

Amino acid is used to rehydrate aged or hardened 25 epidermis. Neutral amino acid (such as glycine, serine, cystine, alanine, threonine, cysteine, valine, phenylalanine, methionine, leucine, tyrosine, proline, isoleucine and hydroxyproline), acidic amino acid (such as aspartic acid, asparagine, glutamine and glutamic acid), 30 and basic amino acid (arginine, histidine and lysine) can be used. Amino acid derivatives include acylsarcosine and its salts, acylglutamic acid and its salts, acyl- β -alanine

- 31 -

and its salts, glutathione, and pyrrolidone carboxylic acid and its salts, as well as oligopeptides such as glutasin, carnosine, gramicidin S, tyrocidin A and tyrocidin B, γ -aminobutyric acid and γ -amino- β -hydroxybutyric acid and its
5 salts.

The content in topical agents for dermatological use should be 0.01-20 w/w%, preferably 0.05-10 w/w%. The skin moisturizing effects may be insufficient if the content is too small. If the content is too large, alteration of amino
10 acid becomes difficult to prevent without increases in its beneficial effects.

0068

15 Amino ethyl compounds, shown by the formula $\text{NH}_2\text{CH}_2\text{CH}_2\text{X}$ (in which X is $-\text{SO}_2\text{H}$ or $-\text{SO}_2\text{SH}$), are used to prevent and relieve rough skin and relieve subduedness.

The content in topical agents for dermatological use should be 0.0001-1.0 w/w%, preferably 0.001-0.3 w/w%.

20

0069

Alkylene diamine carboxylic acid derivatives are used
25 to increase stability of topical agents for dermatological use. Ethylene diamine tetraacetate and its alkali metal salts (such as Na, K and Li salts), alkali earth metal salts (such as Ca and Mg), ammonium salt, and alkanol salts are preferable, but Na salt is most preferable.

30 The content in topical agents for dermatological use should be 0.01-0.5 w/w%, preferably 0.05-0.5 w/w%.

0070

- 32 -

Betaine derivatives are used to increase percutaneous absorption of 4-hydroxyphenyl- α -D-glucopyranoside, and alkyl dimethyl amino acid showed by general formula 13, 2-alkyl-1-carboxy-methyl-1-hydroxyethyl-2-imidazoline shown by general formula 14, N-(3-acylaminopropyl)-N,N-dimethylamino acetate shown by general formula 15, and N-alkyl-N,N-dimethyl-3-amino-2-hydroxypropane sulfonic acid shown by general formula 16 are desirable.

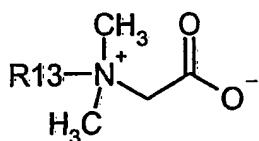
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0071

Acyl methyl taurine is also used to increase percutaneous absorption of 4-hydroxyphenyl- α -D-glucopyranoside and can be shown by general formula 17.

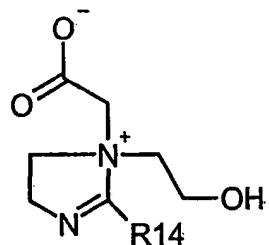
0072

Chemistry 5



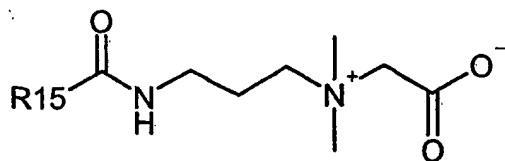
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General formula 13



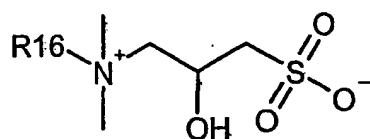
General formula 14

- 33 -

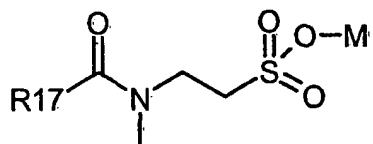


5

General formula 15



General formula 16



10

General formula 17

0073

15 In general formulas 13, 14, 15, 16 and 17, R13 and R16 are normal-chain or branched alkyl groups with 8 to 24 carbon atoms; R14, R15 and R17 are normal-chain or branched alkyl groups with 7 to 23 carbon atoms; M is a univalent or bivalent metal, ammonium, alkanol amine or hydrogen atom.

20

0074

The combined content of betaine derivatives and acyl methyl taurine in topical agents for dermatological use

should be 0.01-30 w/w%, preferably 0.1-20 w/w%.

0075

Fibronectin (cold insoluble globulin) increases
5 whitening effects of 4-hydroxyphenyl- α -D-glucopyranoside used in the present invention.

The suitable content in topical agents for dermatological is 0.000001-0.1 w/w%.

10

0076

Tyrosinase inhibitors are added to enhance the inhibition of tyrosinase activity by 4-hydroxyphenyl- α -D-glucopyranoside or to give greater anti-tyrosinase effects to the topical agents for dermatological use covered by the resent invention by way of synergism with 4-hydroxyphenyl- α -D-glucopyranoside. To obtain tyrosinase inhibitors, cells of *Catharanthus roseus L.* (group of cells or tissue strips such as the root, embryonic axis, and cotyledon of young plants and the root, stem, petiole, flower, and pollen of mature plants) are cultured on medium to which plant growth controlling agents containing plant hormones such as auxin and cytokinin are added in order to induce 20 callus, or tumor tissues are produced using *agrobacterium tumefaciens* or *agrobac-terium rhizogenes*. The callus or tumor tissue is cultured using 4-hydroxyphenyl- α -D-glucopyranoside containing media (such as Murashige-Skoog medium, Linsmaier-Skoog medium, White medium, Gamborg medium, Nitsch medium, Heller medium, Schenk-Hildebrandt medium, Nitzsch-Nitzsch medium, and Kohlenbach-Schmidt medium) and the cultures obtained are homogenized. The 30

transparent fluid deriving from the homogenate obtained is used per se or after drying as a tyrosinase inhibitor.

The content should be adjusted so that appropriate antityrosinase activity is obtained.

5

0077

Hederacoside enhances the whitening effects of the topical agents for dermatological use covered by the 10 present patent as a result of synergism with 4-hydroxyphenyl- α -D-glucopyranoside. Hederacoside is a triterpenoid saponin obtained from extracts of *Sapindus mukurossi* Gaertn. or *Akebia quinata* Decne. Its salts include alkali metal salts such as Na and K salts, ammonium 15 salt, basic amino acid salts, alkanol amine salts, and esters. These extracts can be used as is.

The content in topical agents for dermatological use should be 0.001-20 w/w%, preferably 0.1-5 w/w%.

20 0078

Gymnema saponin enhances the whitening effects of the topical agents for dermatological use covered by the present patent as a result of synergism with 4-hydroxyphenyl- α -D-glucopyranoside. Gymnema saponin is a triterpenoid saponin obtained from extracts of *gymnema inodrum* or *Gymnema sylvestre* R. Br. Its salts include alkali metal salts such as Na and K salts, ammonium salt, basic amino acid salts, alkanol amine salts, and esters. 30 These extracts can be used as is.

The content in topical agents for dermatological use should be 0.001-20 w/w%, preferably 0.1-5 w/w%.

- 36 -

0079

Beat saponin enhances the whitening effects of the topical agents for dermatological use covered by the present patent as a result of synergism with 4-5 hydroxyphenyl- α -D-glucopyranoside. Beat saponin is an oleanolic acid glycoside obtained from beat extracts. Its salts include alkali metal salts such as Na and K salts, ammonium salt, basic amino acid salts, alkanol amine salts, and esters. These extracts can be used as is.

10 The content in topical agents for dermatological use should be 0.001-20 w/w%, preferably 0.1-5 w/w%.

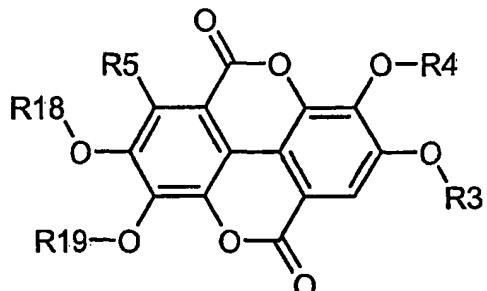
0080

Ellagic acid-related compounds are added to improve 15 stability of the topical agents for dermatological use covered by the present patent and can be shown by general formula 18. Alkali metal salts of ellagic acid-related compounds include Na and K salts.

The content in topical agents for dermatological use 20 should be 0.001-30 w/w%, preferably 0.05-10 w/w%.

0081

Chemistry 6



General formula 18

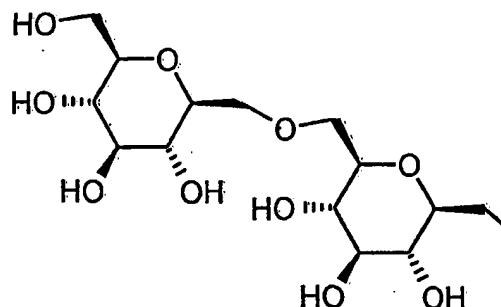
- 37 -

0082

In general formula 18, R18, R19, R20 and R21 are hydrogen atoms, alkyl groups with 1 to 20 carbon atoms (such as methyl group, ethyl group and propyl group), acyl groups with 1 to 20 carbon atoms (such as acetyl group and propionyl group), polyoxy alkylene groups which can be shown by the formula -(C_mH_{2m}-O)_nH (in which m is 2 or 3, n is 1 or a greater integral number, preferably a number between 4 and 50) (such as polyoxyethylene group and polyoxypropylene group), or sugar residues which are shown by general formula 19. R18, R19, R20 and R21 may be the same or different. R22 is a hydrogen atom, hydroxyl group, or alkoxy group with 1 to 8 carbon atoms.

15 0083

Chemistry 7



20

General formula 19

0084

25

Examples of ellagic acid-related compounds and its

alkali metal salts include ellagic acid, 3,4-di-O-methyl ellagic acid, 3,3'-di-O-methyl ellagic acid, 3,3',4-tri-O-methyl ellagic acid, 3,3',4,4'-tetra-O-methyl-5-methoxy ellagic acid, 3-O-ethyl-4-O-methyl-5-hydroxy ellagic acid 5 and amritoside, as well as their alkali metal salts.

These ellagic acid-related compounds can be obtained from natural resources such as strawberry, *Caesalupinia spinosa*, eucalyptus, apple, *Coriaria japonica*, *pinus radiata*, bearberry, pomegranate, *Phyllanthus emblica* L., 10 *Sapium sebiferum* leaf, *Rhus chinensis* leaf, *Acacia catechu* L., *Platycarya strobilacea* leaf, *Terminalia chebula*, *Camptotheca acuminata*, *Polygonum bistorta* L., *Lagerstroemia subcostata*, *Sapium discolor* root, *Sapium discolor* leaf, *Bischofia javanica*, *Lythrum salicaria* L., *Geranium pratense* 15 L., *Euphorbia hirta* L., *Eucalyptus citriodora* leaf, *Euphorbia royleana*, *Psidium guajava* fruit, *Psidium guajava* cortex, *Mangife-ra indica* L., gall, *Syzygium cumini* fruit, *Syzygium cumini* cor-tex, *Phyllanthus emblica* root, *Phyllanthus emblica* cortex, *Phyl-lanthus emblica* leaf, 20 *Agrimonia pilosa* root, *Psidium guajava* leaf, *Sapium sebiferum* root cortex, SHIDOKON (Kanppo name), CHINSYUSO (Kanppo name) and geranium herb.

0085

25

Resorcinol derivatives show blood flow improving effects and cell activation effects. They inhibit the formation of melanin due to UV rays and promote the elimination of melanin. They also prevent the epidermis 30 from drying, promote the skin metabolism, and prevent aging of the skin due to UV rays.

Specifically resorcinol derivatives include 4-n-ethyl resor-cinol, 4-n-butyl resorcinol, 4-n-hexyl resorcinol,

and 4-isoamyl resorcinol.

The content in topical agents for dermatological use should be 0.0001-20 w/w%, preferably 0.01-10 w/w%.

5 0086

Unless otherwise specified, all of the auxiliary agents listed above enhance the whitening effects of the topical agents for dermatological use under the present 10 invention when concur-rently used with 4-hydroxyphenyl- α -D-glucopyranoside. Some of these auxiliary agents also increase the stability and/or safety of the topical agents.

None of these auxiliary agents affects 4-hydroxyphenyl- α -D-glucopyranoside in the topical agents 15 when used with 4-hydroxy-phenyl- α -D-glucopyranoside in the indicated range of the con-tents. They remain stable for a long period of time and show excellent whitening effects. Their contents may be increased or decreased depending on the degree of expected effects. Each of these auxiliary 20 agents can be used alone or in combination with one or more of the other agents.

0087

25 4-hydroxyphenyl- α -D-glucopyranoside used in the present invention is explained below in great detail.

4-hydroxyphenyl- α -D-glucopyranoside is obtained as a result of α -binding of D-glucose with the phenol group of 1,4-dihydro-xybenzene. β -Arbutin, which is obtained as a 30 result of β -binding of D-glucose with the phenol group of 1,4-dihydroxybenzene, is commonly used in topical agents

- 40 -

for dermatological use because of its kin whitening effects. 4-Hydroxyphenyl- α -D-glucopyranoside is not only more effective than β -arbutin but is also more stable and safer when applied to the skin.

5

0088

The content of 4-hydroxyphenyl- α -D-glucopyranoside in topical agents for dermatological use should be 0.01-30
10 w/w%, preferably 0.05-20 w/w% and more preferably 0.1-10 w/w%.

0089

15 4-Hydroxyphenyl- α -D-glucopyranoside can be chemically manufactured, but it can also be obtained by converting 1,4-dihydro-xybenzene into glycoside using enzymes deriving from bacteria. For example, this can be achieved using sucrose as a sugar donor and *Leuconostoc mesenterioides*-derived sucrose phosphorylase as an enzyme.
20

4-Hydroxyphenyl- α -D-glucopyranoside can also be obtained using soluble starch as a sugar donor and *Bacillus subtilis*-derived α -amylase as an enzyme. In this method, the use of amy-lase X-23 makes it possible to efficiently
25 obtain 4-hydroxy-phenyl- α -D-glucopyranoside on an industrial scale.

0090

30 How 4-hydroxyphenyl- α -D-glucopyranoside used in the present invention can be obtained using amylase X-23, a

- 41 -

type of amylase obtained from *Bacillus subtilis*, is outlined below. Amylase X-23 decomposes glucan with α -1,4 bond in the presence of both phenol related compounds and glucan with α -1,4-bond, and transfers sugar to the OH group of phenol related compounds by α -binding. The optimal pH for sugar transfer ranges between 5 and 8. Sugar transfer can be achieved in a stable manner at pH 5.5 and 30-70°C. Refer to Patent No. 2662667 Patent Gazette for greater detail.

10

0091

Other ingredients commonly used for the production of topical agents for dermatological use, including cosmetics and drugs, can be added, if necessary, to topical agents for dermatological use under the present invention. These ingredients include oil, antioxidants, surface active detergents, moisturizing agents, moistening agents, aromatics, water, alcohol, viscous agents, antiseptics, coloring agents, powder, drugs, chelating agents, and pH adjusting agents. These ingredients must be added in amounts which do not qualitatively or quantitatively affect the quality of topical agents for dermatological use covered by the present invention.

25

0092

Topical agents for dermatological use covered by the present invention may be made available in any dosage form, including solutions such as toilet lotion, emulsified preparations such as milky liquid and cream, ointment, viscous gel, dispersion, and powder.

0093

When manufacturing topical agents for dermatological use covered by the present invention in the form of lotion, emulsion and viscous gel, greater efficacy can be obtained by combining the following water-soluble viscous agents with lower alcohol such as ethanol and isopropanol: plant-derived macromolecules (such as gum arabic, tragacanth gum, galactan, Cyamopsis gum, carrageenan, pectin, quince seed (marmelo) extract and brown algae powder), microorganism-derived macromolecules (such as xanthan gum, dextran and pullulan), animal-derived macromolecules (such as collagen, casein, albumin and gelatin), starch (such as carboxymethyl starch and methylhydroxy starch), cellulose (such as methylcellulose, nitrocellulose, ethylcellulose, methylhydroxypropylcellulose, hydroxyethylcellulose, cellulose sulfate, hydroxypropylcellulose, carboxymethylcellulose, crystalline cellulose, cellulose powder), vinyl macromolecules (polyvinyl alcohol, polyvinylmethylether, polyvinylpyrrolidone and carboxyvinyl-polymer), acryl macromolecules (such as polyacrylic acid and its salts and polyacrylimide), organic viscous agents (such as gly-cyrrhizic acid and alginic acid), and inorganic viscous agents (such as bentonite, hecolite, labonite, aluminum silicate mag-nesium and silicic anhydride).

The content of water-soluble viscous agents in topical agents for dermatological use should be 0.01-5 w/w%, preferably 0.1-3 w/w%, while the content of lower alcohol in topical agents for dermatological use should be 0.3-35 w/w%. It is desirable to adjust the ratio of 4-

- 43 -

hydroxyphenyl- α -D-glucopyranoside and lower alcohol
(weight) to 3:1 to 1:3.

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Working examples

4-Hydroxyphenyl- α -D-glucopyranoside used in all examples shown below is obtained by allowing amylase X-23 to act in the presence of 1,4-dihydroxybenzene and 10 maltopentaose. All contents shown below are based on w/w%.

Example 1: toilet lotion

A toilet lotion was prepared by the conventional method using the formula shown below.

15

Propylene glycol	5.0
Ethanol	14.0
POE (20) oleyl ether	0.5
4-Hydroxyphenyl- α -D-glucopyranoside	0.5
2-Hydroxy-4-methoxybenzophenone-5-sodium sulfonate	0.1
Methylparaben	0.1
Citric acid	0.01
Sodium citrate	0.1
Chamomile extract	2.0
Water-soluble placenta extract	2.0
Sodium hyaluronate	0.3
Flavor	0.05
Ion exchanged water	Remainder

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Example 2: emulsion

An emulsion was prepared by the conventional method
5 using the formula shown below.

Stearate	3
Cetyl alcohol	2
Petrolatum	5
Liquid paraffin	10
Polyoxyethylene (10) monooleate ester	2
Polyoxyethyleneglycol 1500	3
Triethanolamine	1
4-Hydroxyphenyl- α -D-glucopyranoside	5
Pantethine-S-sodium sulfonate	10
N'N-dimethyl PABA octyl ester	5.0
Hydroquinone monomethyl ether	0.01
Sodium hydrogen sulfite	1.0
Azelaic acid	0.2
Pyridoxine	0.2
Ion exchanged water	Remainder
Flavor	Q.S.
Antiseptic	Q.S.

0096

10 Example 3: cream

A cream was prepared by the conventional method using
the formula shown below.

Propylene glycol	5.0
Yellow beeswax	4.0

- 45 -

Cetyl alcohol	5.0
Reduced lanolin	5.0
Squalene	36.0
Glyceryl monostearate	2.0
POE (20) sorbitan monolaurate	2.0
Methylparaben	0.1
Ethylparaben	0.15
4-Hydroxyphenyl- α -D-glucopyranoside	1.0
Allantoin	3.0
Japanese angelica root extract	0.2
Crude sugar extract	1.0
Teprenone	1.0
Kojic acid	1.0
Flavor	0.1
Ion exchanged water	Remainder

0097

Example 4: pack

5 A pack product was prepared by the conventional method using the formula shown below.

Polyvinyl alcohol	16.0
Polyethylene glycol	4.0
Propylene glycol	7.0
Ethanol	11.0
Methylparaben	0.1
4-Hydroxyphenyl- α -D-glucopyranoside	7.0
Dihydroxy aluminum allantoinate	3.0
Ascorbic acid	1.0
Nordihydroguaiaretic acid	5.0
Citric acid	0.3

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Sodium citrate	0.7
Flavor	0.1
Ion exchanged water	Remainder

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Example 5: scalp treatment (toilet lotion for scalp
5 treatment)

A toilet lotion for scalp treatment was prepared by the conventional method using the formula shown below.

1,3 butylene glycol	6.0
Polyethylene glycol	4.0
Ethanol	11.0
POE (60) hydrogenated castor oil	2.0
Potassium hydroxide	0.05
Carboxyvinyl polymer	0.2
2-Hexyldecylpalmitate	11.0
Squalene	5.0
Yellow beeswax	0.5
4-Hydroxyphenyl- α -D-glucopyranoside	10.0
Allantoin	4.0
Antiseptic	0.2
Flavor	0.1
Ion exchanged water	Remainder

10 0099

Example 6: ointment

Ointment was prepared by the conventional method using the formula shown below.

- 47 -

Petrolatum	40.0
Stearyl alcohol	15.0
Japan wax	15.0
POE (10) oleate	0.25
Glyceryl monostearate	0.25
4-Hydroxyphenyl- α -D-glucopyranoside	6.0
Allantoin	1.0
Sorbitol	5.0
Propylene glycol	5.0
Gentian extract	0.3
Ion exchanged water	Remainder

0100

5 Example 7: powder

A powder was prepared by the conventional method using the formula shown below.

Tranexamic acid	0.1
Calamine	0.1
Sulfur	0.1
Oil soluble glycyrrhiza extract	1.0
Dextrin	2.0
Talc	95
Decaglycel stearate	1.0
4-Hydroxyphenyl- α -D-glucopyranoside	0.7

10 0101

Example 8: toilet oil

Toilet oil was prepared by the conventional method

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using the formula shown below.

Tocopherol	0.2
4-hydroxycinnamate	0.2
Allantoin	0.5
Ascorbyl palmitate	0.2
4-Hydroxyphenyl- α -D-glucopyranoside	1.0
Retinol acetate	0.3
Evening primrose oil	2.0
Oil soluble glycyrrhiza extract	1.0
Squalene	Remainder

0102

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All topical agents for dermatological use obtained in Examples 1 through 8 showed good skin whitening effects with only slight skin irritation and sensitization potential. They also showed good stability over time.

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Test 1

A clinical trial was conducted using a cream prepared 15 according to the formula shown in Example 3 except that the content of 4-hydroxyphenyl- α -D-glucopyranoside was changed from 1.0 w/w% to 0.5 w/w% and a control cream prepared in accordance with the formula shown in Example 3 except that 4-hydroxyphenyl- α -D-gluco-pyranoside was 20 replaced with β -arbutin.

A total of 12 volunteers (6 men and 6 women aged between 25 and 55 years) were enrolled. The cream covered by the present invention was applied to an area in the

- 49 -

medial side of the right upper arm of 6 volunteers (3 men and 3 women). The β -arbutin-containing control cream was applied to the remaining volunteers. Application was made 3 times a day (every 8 hours) for 7 consecutive days. The 5 application sites were exposed to UV rays of 1 MED (minimum erythema dose) after application 3 times a day starting the first day of application using a UVB light source. The volunteers were crossed over 30 days after completion of the first trial, and the trial was repeated in the same way 10 at another site in the medial part of the right upper arm. The double-blind design was used.

The degree of skin blackening was compared 14 days after starting UV ray irradiation to assess the skin blackening prevention effects with the naked eye. The 15 efficacy was rated using the following 5-degree scale: very effective, effective, slightly effective, ineffective and aggravated.

Results obtained are shown in Table 1.

20 0104

Table 1

	Control	Invented cream
Very effective	1 (8.3%)	3 (25.0%)
Effective	3 (25.0%)	6 (25.0%)
Slightly effective	5 (41.0%)	2 (16.7%)
Ineffective	3 (25.0%)	1 (8.3%)
Exacerbated	0	0

0105

25 The invented cream was more effective than the control cream (whose β -arbutin content was twice as large as that

- 50 -

of 4-hydroxy-phenyl- α -D-glucopyranoside in the invented cream) in preventing skin blackening and no adverse reaction was observed. This finding indicates that the invented cream is an excellent product.

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0106

Effects of the invention

The topical agents for dermatological use covered by
10 the present invention enhance the effects of 4-
hydroxyphenyl- α -D-glucopyranoside due to synergistic
effects because they combine 4-hydroxyphenyl- α -D-
glucopyranoside, which is safe and stable and exerts good
skin whitening effects even when used alone, and various
15 auxiliary agents. Therefore, topical agents for dermatolo-
gical use covered by the present invention show marked
skin whitening effects and blackening prevention effects
and effecti-vely prevent and relieve liver spots and
freckles. They were also shown to be safe and stable and
20 are extremely useful as cosmetics and therapeutic agents.

Claims

1. Topical agents for dermatological use which are
5 characterized by the fact that they contain 4-hydroxyphenyl- α -D-glu-copyranoside and at least one of the following: ascorbic acid and its derivatives, crude drugs and their extracts, hydroxycarboxylic acid and its salts, oil-soluble glycyrrhi-za extract, gentian extract, phenol
10 derivatives and its salts, placenta extract, kojic acid and its derivatives, glucosamine and its derivatives, azelaic acid and its deri-vatives, retinol and its derivatives, pyridoxin and its de-rivatives, tocopherol and its derivatives, vitamin E-nicoti-nate,
15 diisopropylaminedichloroacetate, chitosan and its decomposition products, caffeic acid derivatives, hydroxycin-namate and its derivatives, Umbelliferae plant extracts, mycelial cultures and their extracts, plants leaves and their extracts, plant bark and its extracts, hinokitiol, ginseng extract, sulfur, crude sugar extracts, molasses extracts, mucopolysaccharide, teprenone, nordihydroguaiaretic acid, UV absorbents, γ -pyrone glycoside, hydroxysali-cyclic acid glycoside, hydroxysalicylic acid fatty ester glycoside, biphenyl compounds, ceramides, substances with
20 ceramide-like structures, ether compounds which can be shown by the general formula R31-O-(X-O)_n-R32 (in which R31 and R32 are the same or different normal-chain, branched or cyclic alkyl groups with 1 to 12 carbon atoms, X is alkylene groups with 1 to 12 carbon atoms, n is 0 or 1, and
25 the num-ber of synthetic carbon atoms in R31, R32 and X is 10 to 32), pantothenic acid and its derivatives, sodium hydrogen sulfite, antiinflammatory agents, allantoin and
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its derivatives, amino acid and its derivatives, aminoethyl compounds, alkylene diamine carboxylic acid derivatives, betaine derivatives, acyl methyl taurine, fibronectin, tyrosinase inhibitors, hederacoside and its salts, gymnema saponin, beat saponin and its salts, ellagic acid-related compounds and their alkaline metallic salts, and resorcinol derivatives.

2. Topical agents for dermatological use described
10 in Claim 1 which are characterized by the fact that 4-
hydroxyphenyl- α -D-glucopyranoside is obtained using α -
amylase.

3. Topical agents for dermatological use described
15 in Claim 2 which are characterized by the fact that the α -
amylase is amylase X-23.

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(54) Title: TOPICAL AGENT FOR DERMATOLOGICAL USE CONTAINING 4-HYDROXYPHENYL- α -D-GLUCOPYRANOSIDE

(57) Abstract: The objective of the present invention was to enhance the skin whitening effects and blackening prevention effects and supply safe and stable topical agents for dermatological use. For that purpose 4-Hydroxyphenyl- α -D-glucopyranoside was combined with auxiliary agents such as ascorbic acid and its derivatives, crude drugs and its extracts, hydroxycarboxylic acid and its salts, oil soluble glycyrrhiza extract, gentian extract, phenol derivatives and their salts, placenta extract, kojic acid and its derivatives, glucosamine and its derivatives, azelaic acid and its derivatives, retinol and its derivatives, pyridoxin and its derivatives, tocopherol and its derivatives, chitosan and its decomposition products, caffeic acid derivatives, hydroxycinnamate and its derivatives, Umbelliferae plant extracts, mycelial cultures and their extracts, plant leaves and their extracts.

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CHEM ABS Data, WPI Data, PAJ, BIOSIS, EPO-Internal, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	EP 1 153 602 A (SHISEIDO COMPANY) 14 November 2001 (2001-11-14) page 4, line 29 -page 5, line 9; example 12; tables 2-1,2-2,2-3 ---	1
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 1997:649706 XP002193686 abstract --- -/-	1



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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 1995:275688 XP002193687 abstract & JP 06 284896 A (KURASHIKI BOSEKI KK) 11 October 1994 (1994-10-11) ---	1-3
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 1995:846101 XP002193688 abstract ---	1
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 1994:577883 XP002193689 abstract & JP 06 153976 A (KIKKOMAN) 3 June 1994 (1994-06-03) ---	1
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 1993:175535 XP002193690 abstract & JP 05 000932 A (KURASHIKI SPINNING CO) 8 January 1993 (1993-01-08) ---	1
E	WO 01 60324 A (PENTAPHARM) 23 August 2001 (2001-08-23) the whole document & DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 2001:617782 abstract ---	1
A	DATABASE REGISTRY 'Online! retrieved from STN Database accession no. 84380-01-8/rn XP002193691 abstract -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP 01/06281

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 1153602	A	14-11-2001	JP EP WO	2001240526 A 1153602 A1 0145665 A1		04-09-2001 14-11-2001 28-06-2001
JP 06284896	A	11-10-1994	JP	7036758 B		26-04-1995
JP 6153976	A	03-06-1994		NONE		
JP 5000932	A	08-01-1993		NONE		
WO 0160324	A	23-08-2001	JP AU WO	2001316268 A 3233501 A 0160324 A1		13-11-2001 27-08-2001 23-08-2001